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EXAMINER
SCHWARTZMAN, R

ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
08/726,211

Applicant(s)
Tormo et al.

Examiner
Robert Schwartzman

Group Art Unit
1636



☒ Responsive to communication(s) filed on Nov 13, 1998

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-55 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-42, 44, and 46-55 is/are rejected.

☒ Claim(s) 43 and 45 is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 15

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

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DETAILED ACTION

This Office action is in response to the amendment filed November 13, 1998. New claims 38-55 have been added. Claims 1-55 are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-9, 31, 33-42 and 47-55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is based on the Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph "Written Description" Requirement published in the Federal Register (Volume 63, Number 114, Pages 32639-32645). Claims 1-3, 5-9, 31, 33-42 and 47-55 are drawn to a composition and a method of using a

Approved 1/2/99
George C. Elliott

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polynucleotide that hybridizes to a BCL-2 encoding polynucleotide. The premise of the claimed invention is the ability of the hybridizing polynucleotide to decrease the expression of BCL-2 in a cell, *i.e.*, an antisense effect. The present specification generally suggests regions within the BCL-2 gene which could be targeted by an antisense oligonucleotide. An oligonucleotide consisting of SEQ ID NO:1 is the only specific oligonucleotide disclosed and is the only oligonucleotide demonstrated to have an antisense effect on BCL-2 expression in a cell. Thus, the specification as filed fails to provide adequate written description for the full scope of any oligonucleotide that is capable of inhibiting a BCL-2 transcript. It should be noted that, although antisense oligonucleotides are known to inhibit translation of a given protein, no guidance is given in the specification that would allow the skilled artisan to find, obtain or envision any other composition comprising antisense oligonucleotides possessing the claimed properties since it is unknown what properties, structural or otherwise, said composition must possess for it to decrease the level of BCL-2 in a cell. Without such guidance, the disclosure is not sufficient to describe the claimed genus of antisense oligonucleotides capable of decreasing the level of BCL-2 in a cell and therefore does not describe the claimed genus in such clear, concise and exact terms to show applicants were in possession of the claimed oligonucleotides.

Claim 42 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

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Claim 42 is drawn to a composition comprising an expression construct that encodes a first polynucleotide that hybridizes to a second, BCL-2-encoding polynucleotide, wherein the first polynucleotide is a P-ethoxy oligonucleotide. Since P-ethoxy nucleotides are not naturally occurring molecules and there is no DNA sequence that can specifically encode a P-ethoxy nucleotide it is not clear how the expression construct can encode a P-ethoxy oligonucleotide. The present specification does not provide any direction or guidance as to how to make an expression construct which encodes a P-ethoxy polynucleotide. Therefore, the claim is not enabled.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) a patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-9 and 31-37 remain rejected and new claims 39-41, 48-50 and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evan or Reed or Green *et al.* in view of Tari *et al.* This rejection is maintained for the reasons of record in the previous Office action mailed July 7, 1998.

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To summarize the rejection, Evan, Reed and Green *et al.* each teach antisense oligonucleotides targeted to BCL-2. The oligonucleotide preferably is targeted to the translation initiation site of BCL-2. The antisense oligonucleotide or an expression construct encoding the antisense oligonucleotide can be delivered into a cell as a liposome composition. Evan, Reed and Green *et al.* do not teach liposomes composed of neutral phospholipids. Tari *et al.* teaches compositions comprising an antisense oligonucleotide encapsulated in a liposome made from neutral phospholipids such as dioleoylphosphatidylcholine. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the present invention was made to make a composition comprising an antisense oligonucleotide targeted to BCL-2 encapsulated in a liposome as taught by Evan or Reed or Green *et al.* and to use the liposomal formulations taught by Tari *et al.*, motivated by the teaching of Tari *et al.* that liposomes comprising dioleoylphosphatidylcholine impart improved stability and cellular uptake to the antisense oligonucleotides.

Applicants argue that Tari *et al.* does not suggest the claimed composition as it teaches that both charged (phosphatidylserine) and uncharged (phosphatidylcholine) phospholipids are preferred. Furthermore, Tari *et al.* does not teach BCL-2 antisense oligonucleotides. Thus, Tari *et al.* fails to provide the motivation to select the claimed combination of neutral lipid liposomes and a BCL-2 specific polynucleotide.

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This argument has been fully considered but is not deemed to be persuasive. Although Tari *et al.* does state that both phosphatidylcholine and phosphatidylserine are preferred phospholipids, it goes on to teach that dioleoylphosphatidylcholine (a neutral phospholipid) is particularly preferred lipid. Additionally, all of the working examples (with the exception of one in which a comparison of different phospholipids is made) utilize dioleoylphosphatidylcholine and Tari *et al.* specifically states that dioleoylphosphatidylcholine was one of the easiest lipids to handle and therefore was the lipid of choice (column 6, lines 53-56). Thus, there is ample motivation in Tari *et al.* to use a neutral lipid in the liposome composition. Additionally, it is noted that the present claims, except for those stating “consisting essentially of neutral lipids”, are written with open language and therefore encompass any combination of lipids as long as there is at least some amount of neutral lipids in the composition. Therefore, a teaching of both neutral and charged lipids still reads on the claimed composition. Although Tari *et al.* does not teach a BCL-2 specific polynucleotide it is not relied upon to do so in the present rejection. Evan, Reed and Green *et al.* are relied upon for the teaching of a BCL-2 specific polynucleotide and there is sufficient motivation to combine the teachings of a BCL-2 specific polynucleotide with the liposome composition of Tari *et al.*

Applicants argue that the claimed composition has surprising, unexpected and superior properties since Tari *et al.* does not teach that neutral lipids are selectively less toxic when combined with BCL-2 oligonucleotide or that charged phospholipids are toxic to cells and should

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be avoided in the case of BCL-2 antisense molecules. Furthermore, the demonstration that a neutral liposome combined with BCL-2 oligonucleotide has selective toxicity to target cells compared to compositions that differ by the presence of 30% negatively or positively charged phospholipids shows the high degree of unpredictability in the field and makes the claimed composition not obvious over Tari *et al.*

These arguments have been fully considered but are not deemed to be persuasive. Tari *et al.* teaches that a composition comprising a neutral liposome comprising an antisense oligonucleotide targeted to an oncogene is selectively toxic to cells comprising the oncogene and that empty liposomes are not toxic to the cells (column 6, line 61-column 7, line 16). Therefore, the disclosure in the present application that a composition comprising a neutral liposome comprising an antisense oligonucleotide targeted to an oncogene (albeit a different oncogene than the one used in Tari *et al.*) is selectively toxic to cells comprising the oncogene and that the liposome itself is non-toxic cannot be considered to be a surprising, unexpected or superior result as there is no demonstration of "superiority in a property" or "the presence of a property not possessed in the prior art" or the "absence of an expected property". The fact that liposomes comprising 30% negatively or positively charged phospholipids are toxic to cells is inconsequential as Tari *et al.* already teaches that neutral liposomes are preferred. A showing of unexpected results would have to show that a neutral liposome comprising a BCL-2 oligonucleotide has properties superior to what one of ordinary skill in the art would expect based

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on the prior art teachings, not superior to compositions that are not even taught in the cited art. The unpredictability argument is not persuasive as the liposome part of the composition of the present claims is identical to the liposome part of the composition taught by Tari *et al.* Unless it can be shown that neutral lipid compositions comprising different oligonucleotides have different and unpredictable properties the field of liposomal delivery of oligonucleotides is deemed to be sufficiently predictable to render obvious the present claims drawn to the identical liposome.

Applicants argue that the newly added dependent claims drawn to liposomes consisting essentially of neutral lipids are not obvious over Tari *et al.* as Tari *et al.* teaches both charged and uncharged lipids.

This argument has been fully considered but is not deemed to be persuasive. As discussed above, Tari *et al.* states that a neutral lipid (dioleoylphosphatidylcholine) is particularly preferred and is the easiest to handle. Furthermore, a liposome consisting only of dioleoylphosphatidylcholine is used in all of the working examples. Therefore, Tari *et al.* renders obvious the lipid composition of the newly added claims.

Applicants argue that Evan, Reed and Green *et al.* do not teach or suggest neutral lipids associated with a BCL-2 oligonucleotide. Thus, these references do not make obvious the claimed invention in light of the surprising and unexpected results.

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This argument has been fully considered but is not deemed to be persuasive. Evan, Reed and Green *et al.* are not relied upon to teach the neutral lipids. This is more than adequately taught by Tari *et al.*, along with sufficient motivation to combine these teachings. Additionally, as discussed above, the results disclosed in the present application are not surprising or unexpected over the teachings of the cited references.

Applicants argue that the combined references do not teach or suggest the claimed composition as the motivation to combine the teachings of Evan, Reed or Green *et al.* with Tari *et al.* is based on the incorrect premise that Tari *et al.* teaches the benefits of using liposomes consisting of neutral lipids since Tari *et al.* actually teaches the benefits of liposomes constructed from either charged or uncharged lipids. Furthermore, the benefits taught by Tari *et al.* are not the same as the benefits of BCL-2 oligonucleotide/neutral liposome constructs taught in the present specification. It is therefore inappropriate to combine these references in an attempt to establish a *prima facie* case of obviousness.

This arguments have been fully considered but are not deemed to be persuasive. As stated above, Tari *et al.* teaches that a neutral lipid (dioleoylphosphatidylcholine) is particularly preferred and is the easiest to handle. Furthermore, a liposome consisting only of dioleoylphosphatidylcholine is used in all of the working examples. The fact that Tari *et al.* teaches that phosphatidylserine (an anionic phospholipid) is another preferred embodiment does

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not take away the teaching that a neutral liposome is particularly preferred or the exemplification of the benefits of a neutral liposome. Thus, there is adequate motivation to use neutral lipids. The argument that the cited references cannot be combined because they teach a benefit other than the benefit taught by the present specification is invalid as it is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant (MPEP 2144).

Claims 1-3, 5-8, 10-31 and 33-36 remain rejected and new claims 39, 44, 46, 48-50 and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Abubakr *et al.*, Pocock *et al.* and Cotter *et al.*, all in view of Tari *et al.*

To summarize the rejection, Abubakr *et al.*, Pocock *et al.*, and Cotter *et al.*, taken together, clearly show that treatment of lymphoma cells having a t(14:18) translocation with an antisense oligonucleotide targeted to the translation initiation site of the BCL-2 gene, either before or after administration to SCID mice, results in the inhibition of proliferation of the lymphoma cells and the prevention of lymphoma development in the mice. None of these references teach administration of the antisense oligonucleotide as a composition comprising neutral lipids. Tari *et al.* teaches compositions comprising an antisense oligonucleotide encapsulated in a liposome made from neutral phospholipids such as dioleoylphosphatidylcholine. Tari *et al.* teaches the benefit of using liposomes consisting of neutral lipids for the delivery of

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antisense oligonucleotides, including improved stability of the antisense oligonucleotide compositions under biologic conditions, improved uptake of the composition in cells, improved incorporation efficiency of the oligonucleotides into liposomes and enhanced specific therapeutic effect of the antisense oligonucleotides (column 2, lines 49-56). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the present invention was made to use an antisense oligonucleotide targeted to BCL-2 to inhibit the proliferation of cells having a t(14:18) translocation resulting in overexpression of BCL-2 as taught by Abubakr *et al.*, Pocock *et al.* and Cotter *et al.* and to administer the antisense oligonucleotide as a composition comprising a neutral phospholipid as taught by Tari *et al.*, motivated by the teaching of Tari *et al.* that the neutral lipid composition imparts several benefits on the administration of an antisense oligonucleotide. It further would have been obvious to inhibit the proliferation of a lymphoma cell in a human as effects seen in immunocompromised mouse models of lymphoma and leukemia are recognized in the art to be reasonably predictive of results in humans. In terms of particular volumes, dosages and schedules of administration, one of ordinary skill in the art could practice routine optimization to determine appropriate volumes, dosages and schedules such as those that are claimed when converting treatments developed for mice into equivalent treatments for humans.

Applicants argue that Abubakr *et al.*, Pocock *et al.* and Cotter *et al.* do not mention any lipid for combining with an antisense BCL-2 oligonucleotide. The references therefore are

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irrelevant to the claimed invention. Applicants further argue that Tari *et al.* teaches both anionic and neutral lipids and the premise for the motivation to combine is incorrect.

These arguments have been fully considered but are not deemed to be persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Although Abubakr *et al.*, Pocock *et al.* and Cotter *et al.* do not teach lipid compositions for use with the BCL-2 oligonucleotide these references are not relied upon for that teaching. Tari *et al.* provides sufficient motivation to make and use a neutral liposome/BCL-2 oligonucleotide based on the teaching of an enhanced specific therapeutic effect when antisense oligonucleotides are incorporated into neutral liposomes. Additionally, Tari *et al.* directly compares the effectiveness of free oligonucleotides and neutral liposome-encapsulated oligonucleotides and shows that the liposomal oligonucleotides are far superior in their ability to kill target cells. Thus, one of ordinary skill in the art, reading Tari *et al.*, would clearly be motivated to use neutral liposomes to enhance the effect of antisense BCL-2 oligonucleotides in the treatment of cells having a t(14:18) translocation resulting in overexpression of BCL-2. As discussed above, Tari *et al.* provides a clear teaching for the use of neutral liposomes even though anionic liposomes are mentioned. Therefore, the premise for motivation to combine the references is correct.

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Claims 4 and 32 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Abubakr *et al.*, Pocock *et al.* and Cotter *et al.*, all in view of Tari *et al.* and further in view of Evan.

Abubakr *et al.*, Pocock *et al.*, Cotter *et al.* and Tari *et al.* each are applied as above. These references do not teach an antisense oligonucleotide which comprises the sequence of SEQ ID NO:1. Evan *et al.* teaches the use of an antisense oligonucleotide targeted to BCL-2 to prevent expression of the BCL-2 protein (page 7, lines 10-29). The oligonucleotide preferably comprises the sequence of claimed SEQ ID NO:1 (page 15, lines 16-23). It would have been *prima facie* obvious to one of ordinary skill in the art at the time the present invention was made to make and use an antisense oligonucleotide targeted to the translation initiation site of BCL-2 as taught by Abubakr *et al.*, Pocock *et al.*, Cotter *et al.* and Tari *et al.* and to have the oligonucleotide comprise the sequence of SEQ ID NO:1 as taught by Evan as Abubakr *et al.*, Pocock *et al.*, Cotter *et al.* and Evan each teach the targeting of the antisense oligonucleotide to a region comprising the ATG codon of BCL-2 and all of the references teach an oligonucleotide sequence which comprises at least part of SEQ ID NO:1. Since all of the oligonucleotides overlap and all of them have been shown to be effective they are all equivalent and one of ordinary skill in the art would reasonably expect that any antisense oligonucleotide which comprises SEQ ID NO:1 would work to lower BCL-2 expression.

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Applicants argue that the inclusion of Evan does not make the claimed invention obvious as the primary references do not teach or suggest the claimed invention of the independent claims.

This argument has been fully considered but is not deemed to be persuasive. As discussed above, the primary references make a strong *prima facie* case of obviousness and the addition of Evan clearly teaches the limitation of claims 4 and 32. Thus, the rejection is maintained.

Conclusion

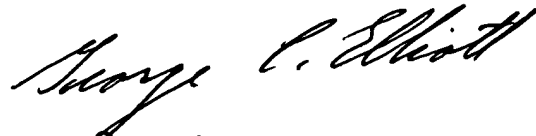
Claims 1-42, 44 and 46-55 are rejected. Claims 43 and 45 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Schwartzman whose telephone number is (703) 308-7307. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached at (703) 308-4003. The fax number for this group is (703) 305-3014.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703)-308-0196.



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Supervisory Patent Examiner
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Robert A. Schwartzman, Ph.D.
December 21, 1998